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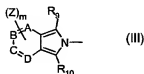
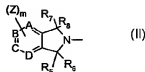
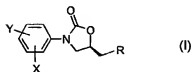
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(54) Title: ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES



(57) Abstract: Bicyclic heterocyclic substituted phenyl oxazolidinone compounds of formula (I); wherein Y is a radical of formulae (II) or (III) in which the substituents have the meaning indicated in the description. These compounds are useful as antibacterial agents.

## ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES

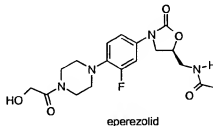
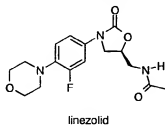
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## FIELD OF THE INVENTION

The present invention relates to the field of phenyl oxazolidinone compounds having antibacterial activity against Gram-positive and Gram-negative bacteria, pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

## BACKGROUND OF THE INVENTION

Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate resistant *Staphylococcus aureus* (GISA), vancomycin-resistant *enterocci* (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As a class, oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.



U.S. Pat. No. 5,792,765 to Riedl et al. discloses a series of substituted oxazolidinones (cyanoguanidine, cyanoamidines, and amidines) useful as antibacterial medicaments.

U. S. Patent No. 5,910,504 to Hutchinson discloses a series of hetero-aromatic ring substituted phenyl oxazolidinones, including indolyl substituted compounds useful as antibacterial agents.

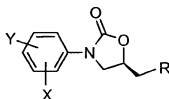
WO 98/54161 (Hester et al.) discloses amides, thioamides, ureas, and thioureas which are antibacterial agents.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives such as linezolid and its analogs which are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiple-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides* spp. and *Clostridia* spp. species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium* spp.

WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones which are useful as antibacterial agents.

## SUMMARY OF THE INVENTION

The invention provides phenyl oxazolidinone compounds of Formula I:



Formula I

wherein:

R is selected from the group consisting of OH, N<sub>3</sub>, OR', O-Aryl, O-Heteroaryl  
OSO<sub>2</sub>R'', -NR'''R''', or



wherein:

- 5 (i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;
- (ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and
- (iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl  
10 having up to 6 carbon atoms which is optionally substituted by cyano or alkoxy carbonyl having up to 4 carbon atoms, -CO<sub>2</sub>-R<sub>1</sub>, -CO-R<sub>1</sub>, -CO-SR<sub>1</sub>, -CS-R<sub>1</sub>, P(O)(OR<sub>2</sub>)(OR<sub>3</sub>), and -SO<sub>2</sub>-R<sub>4</sub>, in which
- 15 R<sub>1</sub> is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl, or acyl each having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon atoms, said alkyl optionally substituted by straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen  
20 atoms, and -NR<sub>5</sub> R<sub>6</sub> in which R<sub>5</sub> and R<sub>6</sub> are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;
- R<sub>2</sub> and R<sub>3</sub> are identical or different and are selected from hydrogen or  
25 straight-chain or branched alkyl having up to 4 carbon atoms; and
- R<sub>4</sub> is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

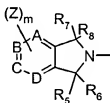
$R_{4a}$  is CN,  $COR_{4c}$ ,  $COOR_{4c}$ ,  $CONHR_{4c}$ ,  $CO-NR_{4c}$ ,  $R_{4d}$ ,  $SO_2R_{4c}$ ,  $SO_2NHR_{4c}$ ,  $SO_2-NR_{4c}$ ,  $R_{4d}$ , or  $NO_2$ ;

5  $R_{4b}$  is H, alkyl,  $OR_{4c}$ ,  $SR_{4c}$ , amino,  $NHR_{4c}$ ,  $NR_{4c}$ ,  $R_{4d}$ , C1-C8-alkylaryl or mono-, di-, tri-, and per-halo C1-C8-alkyl;

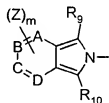
$R_{4c}$  and  $R_{4d}$  are independently selected from H, alkyl, aryl, or in the case of any  $NR_{4c}R_{4d}$  group  $R_{4c}$  and  $R_{4d}$  taken together with the nitrogen atom to which they are attached form an unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub> alkoxy, thio-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub> alkyl-amino, di(C<sub>1-8</sub>-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C<sub>1-8</sub> alkyl-CO-O-, C<sub>1-8</sub> alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, C<sub>3-6</sub> cycloalkyl, C<sub>1-8</sub> alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, C<sub>1-8</sub> alkoxy and C<sub>1-8</sub> acyloxy; and

20 Y is a radical of Formulae II or III:



Formula II



Formula III

wherein

30

$R_5$ ,  $R_6$ ,  $R_7$ , and  $R_8$  are each independently H, alkyl, CN, nitro, C<sub>1-8</sub> alkyl, halo-C<sub>1-8</sub>-alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or  $R_5$  and  $R_6$  and/or  $R_7$  and  $R_8$  together form an oxo group;

R<sub>9</sub>, and R<sub>10</sub> are each independently H, halogen, alkyl, OH, CN, mercapto, nitro, C<sub>1-8</sub> alkyl, halo-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub> alkoxy, thio-C<sub>1-8</sub>-alkyl, amino, C<sub>1-8</sub>-alkyl-amino, di(C<sub>1-8</sub>-alkyl)-amino, formyl, carboxy, alkoxycarbonyl, C<sub>1-8</sub>-alkyl-CO-O-, C<sub>1-8</sub>-alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or amine;

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O, and N;

Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl, said dialkylamino consisting of straight-chain or branched alkyl having up to 6 carbon atoms or phenyl or constituting a ring of 2 to 5 carbons having 0 to 2 atoms selected from S, O and N or alkoxy, or NHCO-(C<sub>1</sub>-C<sub>8</sub>-alkyl); and

m is 0 or 1,

and the pharmaceutically acceptable salts and esters thereof.

Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound of Formula I.

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a

prophylactically effective dose of the pharmaceutical composition of a compound of Formula I.

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

## DETAILED DESCRIPTION

Relative to the above description of the phenyl oxazolidinone compounds of the present invention, the following definitions apply.

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl" may be straight or branched groups with 1-8 carbon atoms.

15

"Acyl" means an organic radical having the designated number of carbon atoms, derived from an organic acid by the removal of a hydroxyl group having the formula RCO, as in the case of acetyl where R is CH<sub>3</sub>.

20

"Aryl" is an unsubstituted carbocyclic aromatic group including, but not limited to, phenyl, 1- or 2-naphthyl and the like. "Heteroaryl" refers to a cyclic aromatic radical having from five to ten atoms in the ring; where one to three ring atoms are independent heteroatoms such as S, O, and N, and the remaining ring atoms are carbon, for example, a pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thienyl, furanyl, quinolinyl, or isoquinolinyl, radical and the like.

25

"Substituted aryl" or "substituted heteroaryl" refers to an aryl or heteroaryl substituted by independent replacement of 1-3 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, C<sub>1-8</sub>-alkyl, halo-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy, thio-C<sub>1-8</sub>-alkyl, amino, C<sub>1-8</sub>-alkyl-amine, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, formyl, carboxy, alkoxycarbonyl, C<sub>1-8</sub>-alkyl-CO-O-, C<sub>1-8</sub>-alkyl-CO-NH-, or carboxamide. Further, substituted-heteroaryl may be substituted with a

mono-oxo to give, for example, a 4-oxo-1-H-quinoline. Substituted-heteroaryl may also be substituted with a substituted-aryl or a second substituted-heteroaryl to give, for example, a 4-phenyl-imidazol-1-yl or a 3-pyridinyl-imidazol-1-yl, and the like.

5

The term "halo" or "halogen" means fluoro, chloro, bromo and iodo. (mono-, di-, tri-, and per-) halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen. P denotes phosphorus.

10

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

20

The phrase "pharmaceutically acceptable salts" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicylic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH,  $\text{Ca}(\text{OH})_2$ ,  $\text{Al}(\text{OH})_3$ , piperidine, morpholine, ethylamine, triethylamine and the like.

30



Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

- 5           The term "subject" includes, without limitation, any animal or artificially modified animal. In the preferred embodiment, the subject is a human.

- The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available  
10   antimicrobial agent at its routine, effective concentration.

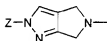
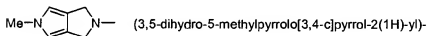
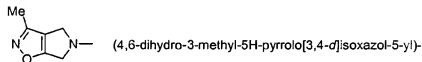
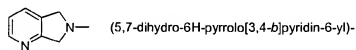
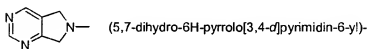
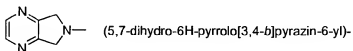
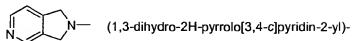
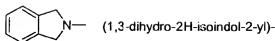
- The compounds of the present invention possess antibacterial activity against Gram-positive and certain Gram-negative bacteria. They are useful as antibacterial agents for the treatment of bacterial infections in humans and  
15   animals. Particularly, these compounds have antimicrobial activity against *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *Moraxella catarrhalis*, and *H. influenzae*. More particularly, these compounds are useful against resistant bacteria such as MRSA and GISA, and have a low susceptibility to acquired resistance mechanisms. Compounds of Formula I  
20   which are most preferred for such purposes are those in which R is any of the following:



In addition Compounds of Formula I which are most preferred for such purposes are those in which Y is any of the following:



isoindolone-;



5

Particular examples of the present invention include the following compounds:

10

*N*-[[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

*N*-[[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

5        *N*-[[[(5*S*)-3-[3-Fluoro-4-(5-oxido-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

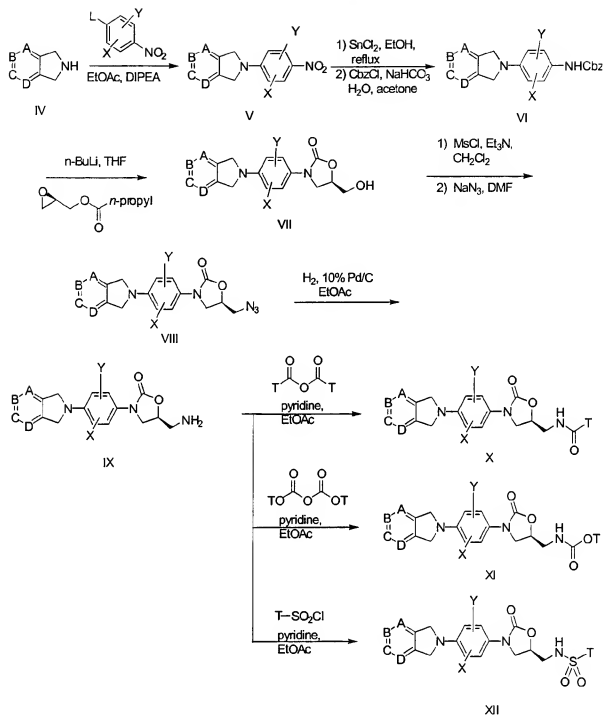
*N*-[[[(5*S*)-3-[4-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

10        *N*-[[[(5*S*)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(5*R*)-3-[4-(5,7-Dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone.

The compounds of Formula I that are the subject of this invention may be prepared from readily available starting materials such as isoindole (Gawley  
15 et al., *J. Org. Chem.*, 1988, 53:5381), 6,7-dihydro-5*H*-pyrrolo[3,4-*c*]pyridine and 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (US Pat. No. 5,371,090 to Petersen et al.) in accordance with synthetic methods well known in the art. Representative procedures are outlined in Scheme I-V:

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Scheme I

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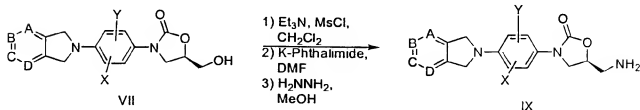
In accordance with Scheme I, bicyclic heterocycles of general formula IV are treated with a substituted nitrobenzene derivative (L is an appropriate leaving group such as a halogen of trifluoromethanesulfonyloxy) in a suitable base

and solvent, such as diisopropylamine and ethyl acetate, to give the substituted nitrophenyl compound V.

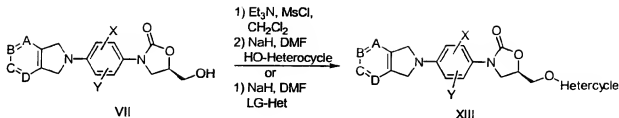
The nitrobenzene derivative V is then reduced to the aniline by an appropriate reaction, for instance by treatment with  $\text{SnCl}_2$  or by catalytic hydrogenation in the presence of a suitable catalyst, such as palladium on carbon. The aniline is then treated with benzyl or methyl chloroformate and sodium bicarbonate to form the corresponding benzyl or methyl carbamate derivative VI.

The Cbz aniline VI is then deprotonated with a lithium base such as *n*-butyllithium and reacted with (R)-glycidyl butyrate to afford the oxazolidinone VII. The hydroxymethyl group can then be converted to an amide as shown in Scheme I by preparation of the mesylate, conversion to azide VIII, and reduction to amine IX by an appropriate procedure such as hydrogenation. Alternatively displacement of a mesylate (Scheme II) or appropriate leaving group such as tosylate or chlorine with potassium phthalimide and removal of the phthaloyl protecting group by hydrazinolysis would provide amine IX. The amine IX can be converted to amide X by an acylation reaction using techniques known in the art, such as treatment with acetic anhydride in the presence of a base such as pyridine. Alternatively, amine IX can be converted to a carbamate XI by treatment with methylchloroformate and pyridine, or reacted with a sulfonyl chloride in an inert solvent in the presence of an organic base like pyridine to form a sulfonamide XII

Scheme II



## Scheme III



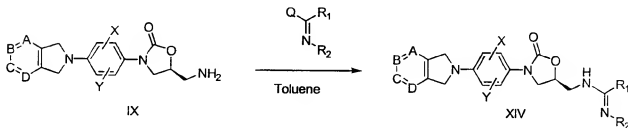
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For the formation of oxazolidinone in which  $\text{R} = \text{O-Heteroaryl}$  (XIII), the oxazolidinone carbinol VII can be converted to the corresponding mesylate or other appropriate leaving group and reacted with HO-Het (a suitable hydroxyl containing heterocycle), either in the presence of base or with HO-Het as a preformed alkoxide, in an appropriate solvent, for example DMF or acetonitrile (Scheme III). Alternatively, Mitsunobu conditions can be used to couple VII with HO-Heterocycle by treating with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in an appropriate solvent, such as THF, at a suitable temperature, preferably room temperature. Reaction conditions and leading references can be found in Gravestock et al, WO99/64416.

Furthermore, by treating VII with a suitable, non-nucleophilic base, for example NaH, the displacement of a leaving group (LG), such as chlorine or bromine, can be effected from an appropriately reactive aza-heterocycle (LG-Het)(Scheme III).

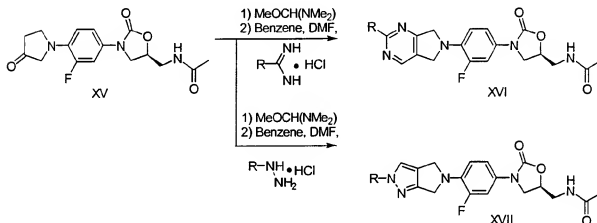
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## Scheme IV



Compounds of structure XIV can be prepared as shown in Scheme IV. Amine IX can be converted to various functionalized amidines by reaction with activated imines, where Q is a leaving group such as methylthio or methoxy, in a suitable solvent, for example toluene or methanol, with or without a catalyst (such AgNO<sub>3</sub>) present at a temperature range of 0-110 °C.

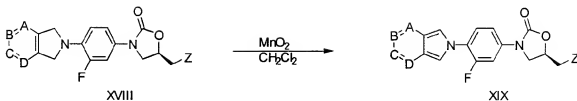
Scheme V



- In accordance with Scheme V pyrrolidinone XV (prepared as in WO96/13502) is first reacted with methoxy-bis(dimethylamine) or other activated dimethylformamide reagent and, second, heated in a suitable solvent (for example DMF and benzene) with either substituted amidines, to form pyrrolopyrimidines oxazolidinones such as XVI, or substituted hydrazines, to form pyrrolopyrazole oxazolidinones such as XVII. Formation of the enamine, alkoxymethylene or alkoxycarbonyl derivatives of pyrrolidinone XV, according to Brighty et al in US 5037834A, would also allow access to these systems.

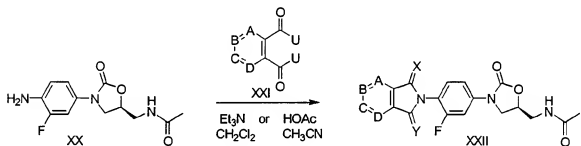
Scheme VI





As shown in Scheme VI compounds with the structure XIX can be achieved by oxidation of the various compounds, XVIII, using an appropriate oxidant (for example manganese dioxide, peroxyacetic acid, DDQ or air) in a suitable solvent such as methylene chloride.

Scheme VII



Oxo-derivatives of structure XXII in Scheme VII, (X = O, Y = H<sub>2</sub> or X = H<sub>2</sub>, Y = O) can be constructed by reacting 1,2-aryl dicarboxaldehydes (where XXI, U = H) with aniline XX (prepared as in WO96/23788) in the presence of acids, such as acetic acid, in a suitable solvent such as methylene chloride. The di-oxo-derivatives (structure XXII where X = Y = O) are prepared from the reaction of aniline XX with selected 1,2-aryl dicarbonyl reagents with a suitable leaving group (XXI where U = Cl, Br, etc).

#### Definitions

All temperatures are in degrees Centigrade

Brine refers to an aqueous saturated sodium chloride solution

DMF refers to N,N-dimethylformamide

THF refers to tetrahydrofuran

Cbz refers to carbobenzyloxy

n-BuLi refers to n-butyl lithium

5 MS refers to mass spectrometry expressed as m/e or mass/charge unit

[M + H] refers to the positive ion of a parent plus a hydrogen atom

Ether refers to diethyl ether

rt refers to room temperature

Mp refers to melting point

10 CH<sub>2</sub>Cl<sub>2</sub> refers to methylene chloride

NaOH refers to sodium hydroxide

MeOH refers to methanol

EtOAc refers to ethyl acetate

ppt refers to a precipitate

15

These compounds have antimicrobial activity against susceptible and drug resistant bacterial pathogens such as *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *S. pyogenes*, *Enterococcus spp.*, *Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram-positive cocci such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

25

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically--Fourth Edition", which is incorporated herein by reference.

30

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the

5 wells is approximately  $5 \times 10^4$  CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at  $35^\circ\text{C}$  for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The

10 amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 1, some compounds of the present invention were tested against a variety of pathogenic bacteria resulting in a range of activities, from 1 to  $\geq 128$   $\mu\text{g/mL}$  depending on the organism tested. *S. aureus*

15 OC2878 is a MRSA and *E. faecium* OC3312 is a vancomycin resistant enterococcus.

Table 1. MIC Values of Some Compounds of Formula I

Compound No.	MIC (mg/mL) in Test Strains		
	<i>S. aureus</i> OC4172	<i>S. aureus</i> OC2878	<i>E. faecium</i> OC3312
1	2	2	2
2	2	1	4
3	0.5	0.25	0.5
4	1	0.5	1
5	>32	>32	>32
6	64	32	32
7	>32	8	16
8	8	4	8
9	>32	>32	>32
10	>32	8	64
11	2	1	2
12	8	2	4

13	2	1	2
14	32	16	16
15	2	2	2
16	8	8	8
17	4	2	2
18	16	16	16
19	8	4	8
20	4	2	4
21	>64	>64	>64
22	2	2	2
23	8	8	8
24	8	8	8
25	64	>128	32
26	1	0.5	1
27	8	4	8
28	0.5	0.5	0.5
29	>32	8	16
30	>128	>128	>128
31	>16	>16	>16
32	4	2	2
33	32	32	32
34	8	2	4
35	0.5	0.25	2
36	1	0.5	1
37	1	1	0.5
38	2	2	1
39	1	2	1
40	1	1	1
41	2	2	2
42	2	2	2
43	1	1	1
44	1	1	1

45	4	4	4
46	4	4	8
47	32	16	32
48	8	8	8
49	16	4	8

This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in a subject having conditions caused by or contributed to by bacterial infection, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention. The terms of "treating" and "treatment" include administering, either simultaneously, separately or sequentially, a pharmaceutically effective amount of a composition containing one or more of the compounds disclosed herein to a subject that desires inhibition of bacterial growth. The pharmaceutically effective amount of the compound used to practice the present invention for treatment varies depending on the manner of administration, the age, weight, and general health of the subject treated, and ultimately will be decided by physicians or veterinarians.

The compounds of the present invention may be administered to a subject such as a human by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route may vary with, for example, the condition of the recipient as well as the ease of preparation and administration.

25

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms

as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene

glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

5           The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be  
10       preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

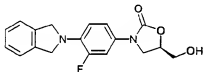
15           The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of  
20       animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid  
25       pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

30           The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

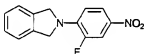
### Example 1

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone



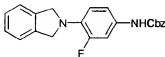
Isoindoline was synthesized employing the method of R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar *J. Org. Chem.* 1988, 53, 5381.

Step 1:



To 3,4-difluoronitrobenzene (3.02 mL, 27.3 mmols) in ethyl acetate at rt was added diisopropylethylamine (5.03 mL, 28.9 mmols) and then isoindoline (3.50 g, 29.4 mmols) and stirred overnight. A yellow precipitate (ppt) formed and was collected on a filter, washed with water and ether and dried in a vacuum oven (30°C) to provide the product as a bright yellow solid (6.69 g, 95% yield). Mp = 200-202 °C. MS (M + 1) = 327 m/z.

Step 2:





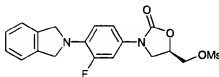
To the above nitro compound (2.62 g, 10.2 mmols) in ethanol (100 mL) was added  $\text{SnCl}_2$  (9.84 g, 50.9 mmols) and was refluxed for 16 hrs. After cooling to rt the reaction mixture was added to 10% aq. NaOH (300 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (6x50 mL). The combined organic washings were washed with brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated to give 2.63 g of an olive green solid (aniline), which was used without further purification. To this aniline in acetone (150 mL) and water (20 mL) was added  $\text{NaHCO}_3$  (1.84 g, 21.9 mmols) and then benzylchloroformate (1.68 mL, 11.8 mmols). After stirring overnight the mixture was poured into ice water (100 mL) and the resulting tan precipitate was collected on a filter, washed with water and dried in a vacuum to give the Cbz aniline as a tan solid (3.50 g, 95% yield). Mp =  $146-148^\circ\text{C}$ . MS ( $M + 1$ ) = 363 m/z.

#### Step 3:

To the above Cbz aniline (0.74 g, 2.04 mmols) in THF (10 mL) at  $-78^\circ\text{C}$  was added *n*-BuLi (2.5 M, 0.82 mL, 2.05 mmols) dropwise. After stirring for 40 min, (R)-glycidyl butyrate (0.31 mL, 2.10 mmols) in THF (0.5 mL) was added dropwise and the resulting mixture was allowed to warm to RT overnight. A white precipitate had formed and was collected on a filter and washed with water and ether. Chromatography on silica gel with 25% ethyl acetate/hexane as eluent provided the product as a white solid (0.58 g, 87% yield). MS ( $M + 1$ ) = 329 m/z.

#### Example 2

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-[[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

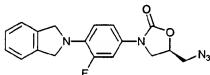


To the oxazolidinone carbinol from Example 1 (0.58 g, 1.78 mmols), in DMF (10 mL) and acetonitrile (10 mL) at  $0^\circ\text{C}$  was added triethylamine (0.74 mL, 5.31 mmols) and, after 10 min, methanesulfonyl chloride (0.28 mL, 3.62 mmols). After allowing the reaction mixture to warm to RT over an hour

starting material was still present so cooling and addition of triethyl amine (0.37 mL, 2.65 mmols) and methanesulfonyl chloride (0.14 mL, 1.81 mmols) was repeated. The mixture was poured into water (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (6 X 20 mL), washed with brine (4 x 10mL), dried over  $\text{Na}_2\text{SO}_4$ , concentrated to afford the crude product as a brown oil (0.95 g). MS ( $M + 1$ ) = 407 m/z.

### Example 3

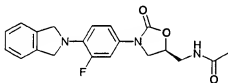
(5*R*)-5-(Azidomethyl)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxazolidinone



To the mesylate from Example 2 (0.95 g, 1.78 mmols) in DMF (25 mL) was added sodium azide (0.47 g, 7.23 mmols) and heated to 70°C for 16 hrs. After cooling to rt water was added and the mixture extracted with ethyl acetate (6X25 mL), washed with brine (4x10 mL), dried over  $\text{Na}_2\text{SO}_4$ , concentrated to give 0.48 g of a tan solid. MS ( $M + 1$ ) = 354 m/z.

### Example 4

*N*-[[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

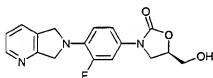


Compound 1

The azide from Example 3 in ethyl acetate (25 mL) was placed in a Paar flask and nitrogen bubbled through for 15 min whereupon 10% Pd/C (0.15 g, 0.14 mmol) was added. The mixture was pressurized with 50 psi of  $\text{H}_2$  (g) and shaken for 16 hrs whereupon an additional amount of 10% Pd/C (0.15 g, 1.4 mmols) was added and the mixture shaken for an additional 6 hrs (at this

point MS ( $M + 1$ ) = 328  $m/z$ ). After placing the mixture under nitrogen, pyridine (0.22 mL, 2.72 mmol) and then  $Ac_2O$  (0.51 mL, 5.30 mmol) were added and the mixture stirred for 2 hrs. The mixture was filtered through celite, washing with ethyl acetate (100 mL), concentrated, and chromatographed on silica (gradient elution 1%-5%  $MeOH/CH_2Cl_2$ ) and then triturated with ethyl acetate (3X3 mL) to give 0.19 g of a white solid (Compound 1, 29% yield for 4 steps).  $Mp = 240-242^\circ C$ . MS ( $M + 1$ ) = 370  $m/z$ .

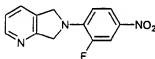
### Example 5



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#### Compound 2

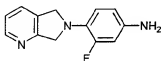
##### Step 1:



6,7-Dihydro-6-(2-fluoro-4-nitrophenyl)-5H-pyrrolo[3,4-b]pyridine: To 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride salt (as described by Petersen, et al. (Bayer) EP0520277A2)(42.8 g, 222 mmols) in DMF (1.2 L) was added 2,4-difluoronitrobenzene (25 mL, 224 mmols). The mixture was heated to  $60^\circ C$  and DIPEA (195 mL, 1.12 mols) was added dropwise from an addition funnel over 2 hrs. After heating overnight the reaction mixture was cooled to rt, poured into water (3 L), filtered and dried in a vacuum oven ( $50^\circ C$ ) to provide a yellow-green solid (53.8 g, 94% yield). MS ( $M + 1$ ) = 260  $m/z$ .

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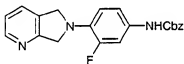
##### Step 2:



6,7-Dihydro-6-(2-fluoro-4-aminophenyl)-5H-pyrrolo[3,4-b]pyridine

To the above nitro compound (53.8 g, 208 mmol) in THF (175 mL) and methanol (600 mL) was added ammonium formate (59.0 g, 907 mmol). Nitrogen was bubbled through the reaction for approximately 30 minutes whereupon 10% Pd/C (2.20 g, 21 mmols) was added. After stirring overnight at rt under an atmosphere of nitrogen the reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol (400 mL), and concentrated to a volume of ca. 200 mL. Water (300 mL) was added and the mixture extracted with ethyl acetate (5X200 mL). The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and utilized directly in the next step without further purification. MS (M + 1) = 230 m/z.

## Step 3:



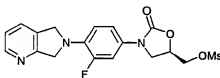
6,7-Dihydro-6-(2-fluoro-4-(Aminocarbonylbenzyl)phenyl)-5H-pyrrolo[3,4-b]pyridine The above aniline (~208 mmols) in acetone (1 L) and water (160 mL) was cooled to 0°C whereupon sodium bicarbonate (37.4 g, 445 mmols) was added followed by the dropwise addition of benzylchloroformate (34.2 mL, 228 mmols). The reaction mixture was allowed to warm to room temperature and stirred overnight whereupon a ppt formed. The reaction was poured into ice water (2 L) and the resulting precipitate was collected by filtration. The solid was washed with water and dried in a vacuum oven (50°C) to afford the Cbz derivative (73.0 g, 97% yield) as a salmon colored powder. MS (M + 1) = 364 m/z.

## Step 4:

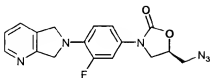
(Compound 2). The above Cbz derivative (40.8 g, 112 mmols) in THF (1 L) was cooled to -78°C under a nitrogen atmosphere. To this mixture was added n-BuLi (2.5 M, 45.8 mL, 114.5 mmols) dropwise via syringe over fifteen minutes. The reaction was warmed to room temperature and allowed to stir

for 45 minutes before again being cooled to  $-78^{\circ}\text{C}$ . At this point (R)-glycidyl butyrate (17.2 mL, 117 mmols) was added and the reaction mixture allowed to warm to rt overnight during which time a precipitate formed. The ppt was collected, washed with several portions of ether (5X100 mL) and dried in a vacuum oven ( $50^{\circ}\text{C}$ ) to afford 40.6 g of the ether solvate of the lithium alkoxide as a tan fluffy powder. This material was then washed with several portions of water (4X200 mL) and dried in a vacuum oven ( $50^{\circ}\text{C}$ ) to afford the oxazolidinone alcohol (34.1 g, 92% yield) as a tan granular solid. Mp =  $208-212^{\circ}\text{C}$ , decomp. MS (M + 1) = 330 m/z.

### Example 6



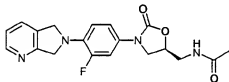
Oxazolidinone Mesylate. The above oxazolidinone carbinol (from Example 4) (33.8 g, 103 mmols) was suspended in DMF (1.25 L, previously degassed with nitrogen) at rt under a nitrogen atmosphere. Triethylamine (50 mL, 360 mmols) was added followed by the dropwise addition of methanesulfonyl chloride (13.5 mL, 174 mmols). After stirring for 3 hrs the reaction mixture was poured into water (200 mL) and methylene chloride (1 L) added. A ppt was filtered off, washed with water (3X200 mL) and dried in a vac oven ( $50^{\circ}\text{C}$ ) to afford the mesylate as a tan solid (28.1 g, 67%). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to also afford the mesylate (11.7 g, 28% yield) as a tan solid. Both were characterized with MS (M + 1) = 408 m/z.

**Example 7**

- 5    Oxazolidinone Azide. The above mesylate (from Example 5) (27.8 g, 68.2 mmols) and sodium azide (17.7 g, 271 mmols) in anhydrous DMF (1 L), previously degassed with nitrogen, were heated 95 °C for 6 hr under a nitrogen atmosphere. After cooling, the mixture was poured into stirred ice water (2 L) and formed a flocculant white ppt. The ppt was collected on a filter and
- 10    washed with water (4X200 mL), dried in a vac oven (50 °C) to afford the azide as a light beige solid (22.7 g, 94% yield). Mp = 175-180 °C, decomp. MS (M + 1) = 355 m/z.

**Example 8**

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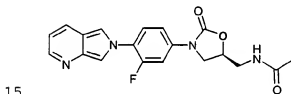
Compound 3

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- Oxazolidinone Acetamide. The above azide (from Example 6)(21.67 g, 61.16 mmol) dissolved in DMF (400 mL) and THF (500 mL) was degassed with nitrogen for 30 minutes whereupon 10% Pd/C (4.74 g, 4.4 mmols) was added and the reaction hydrogenated on a Parr apparatus (60 psi of hydrogen) for
- 25    14 hr. The reaction mixture was removed from the Parr apparatus and placed under a nitrogen atmosphere whereupon pyridine (5.44 mL, 67.3 mmols) and acetic anhydride (6.35 mL, 67.3 mmols) were added. After stirring for 1 hr the

reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol and then copious amounts of 50% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (ca. 2 L). The filtrate was evaporated to afford the crude acetamide in DMF. The mixture was slowly added to water (2 L) and the ppt collected on a filter, washed with  
5 water (5X400 mL) and dried in a vac oven (50 °C) to provide the acetamide as an analytically pure white solid (14.2 g, 63% yield). The combined filtrates were extracted with methylene chloride (5X200 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Water was added to the residue and the resulting ppt was filtered off and dried in a vac oven (50 °C) to afford a second crop of the  
10 acetamide as a light tan, fluffy solid (5.61 g, 25%). For the analytically pure material Mp = 229-230 °C, decomp. MS (M + 1) = 371 m/z.

### Example 9

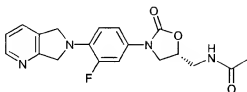


Compound 4

The above acetamide from Example 8 (2.51 g, 6.78 mmols) was taken up in CH<sub>2</sub>Cl<sub>2</sub> and MnO<sub>2</sub> added (23.9 g, 234 mmols). After stirring overnight the reaction mixture was filtered through celite, concentrated and chromatography  
20 on silica with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a light yellow solid (0.48 g, 19% yield). Mp = 220-225 °C decomp. MS (M + 1) = 369 m/z.

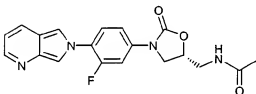
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### Example 10



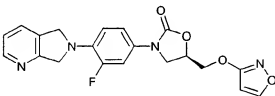
Compound 5

- Compound 5 was prepared as in Example 8 except (S)-glycidyl butyrate was employed in the oxazolidinone formation. The product was isolated as a light tan solid. Mp = 227-230 °C decomp. MS (M + 1) = 371 m/z.

**Example 11**

- Compound 6 oxidized enantiomer

Compound 6 was prepared as in Example 9 and isolated as a light yellow solid. Mp = 181-185 °C decomp. MS (M + 1) = 369 m/z.

**Example 12**

Compound 7

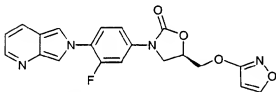
- To 5-hydroxyisoxazole (prepared as in *Chem Pharm Bull* 1966, 14(11), 1277) (0.174 g, 2.04 mmols) in DMF was added NaH (60% in oil) (0.105 g, 2.62 mmols). After stirring for 30 min the mesylate (from Example 6) (0.744g, 1.82



mmols) was added in one portion and the mixture stirred at 60 °C overnight. After cooling to rt water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a white solid (0.140 g, 19 % yield). Mp = 182-185 °C.

5 MS (M + 1) = 397 m/z.

### Example 13



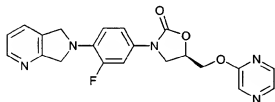
Compound 8

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To the above oxazolidinone (from Example 12) (0.264 g, 6.66 mmols) was taken up in CH<sub>2</sub>Cl<sub>2</sub> and MnO<sub>2</sub> added (1.66 g, 16.2 mmols) in two portions over two days. After stirring for two days the reaction mixture was filtered through celite, concentrated and chromatographed on silica with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a light yellow solid (0.086 g, 32% yield). Mp = 133-135 °C. MS (M + 1) = 395 m/z.

15

### 20 Example 14



Compound 9

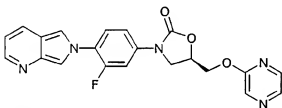
To NaH (60% by wt in oil)(0.03 g, 0.76 mmol) in DMF (5 mL) was added oxazolidinone carbinol (from Example 5) (0.23 g, 0.71 mmol) in four portions.

25 After stirring for 30 min 2-chloropyrazine (0.065 mL, 0.71 mmol) was added

via syringe and stirred overnight at rt. Water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a white solid (0.067 g, 23 % yield). Mp = 225-230°C. MS (M + 1) = 408 m/z.

5

### Example 15



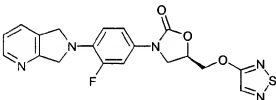
Compound 10

10

The above oxazolidinone (from Example 14) (0.024 g, 0.058 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added MnO<sub>2</sub> (0.07 g, 0.7 mmol). After stirring overnight the reaction mixture was filtered through Celite and concentrated to afford the product as a very light yellow solid (0.015 g, 64% yield). Mp = 192-194°C.

15 MS (M + 1) = 406 m/z.

### Example 16



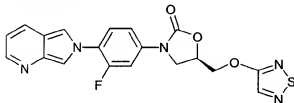
20 Compound 11

To a suspension of the oxazolidinone carbinol (prepared in Example 5) (330 mg, 1.0 mmol), triphenylphosphine (260 mg, 1.1 mmols) and 4-hydroxy-1, 2, 5-thiadiazole (100 mg, 1.0 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]) in THF (8 mL) was added diisopropylazodicarboxylate (0.20 mL, 1.1 mmols). After stirring overnight at rt the reaction mixture was filtered, washed

25

with methanol, and air dried to afford a yellow crystalline solid (60 mg, 15% yield). Mp = 185-187 °C. MS (M + 1) = 414 m/z.

### Example 17



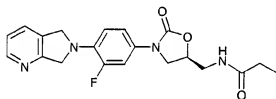
5

### Compound 12

To the oxazolidinone (prepared in Example 16) (160 mg, 0.39 mmol) suspended in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added MnO<sub>2</sub> (four additions of 150 mg over four days). The reaction mixture was filtered through a plug of Celite, washed with CH<sub>2</sub>Cl<sub>2</sub> (15 mL), and concentrated under reduced pressure to afford the product as a white crystalline solid (63 mg, 40% yield). Mp = 185-188 °C. MS (M + 1) = 412 m/z.

15

### Example 18

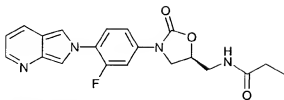


### Compound 13

20

To the amine (as prepared in Example 8) (100 mg, 0.30 mmol) and potassium carbonate (100 mg, 0.72 mmol) suspended in methanol (1.0 mL), was added propionyl chloride (50 mg, 0.54 mmol). After stirring overnight at 80 °C the reaction mixture was cooled and water was added. A precipitate was filtered off, washed with methanol and air dried to afford the product as a brown crystalline solid (15 mg, 13 % yield). Mp = 110-112 °C. MS (M + 1) = 385 m/z.

25

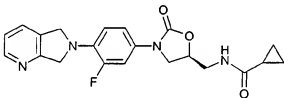
**Example 19**

Compound 14

5

To the amide (prepared in Example 18) (15 mg, 0.04 mmol) suspended in  $\text{CH}_2\text{Cl}_2$  (1.0 mL), was added  $\text{MnO}_2$  (200 mg) at rt. After stirring overnight, the reaction mixture was filtered through a plug of Celite, washed with  $\text{CH}_2\text{Cl}_2$  (10 mL), and concentrated under reduced pressure to afford the product as an

10 light brown crystalline solid (1.6 mg, 8 % yield). MS ( $M + 1$ ) = 383 m/z.

**Example 20**

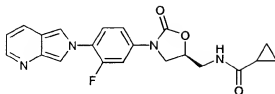
15 Compound 15

To the amine (as prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added cyclopropyl carbonyl chloride (120 mg, 1.15 mmols). After stirring at rt

20 overnight, the reaction mixture was filtered, rinsed with methanol, and then concentrated to dryness under reduced pressure. The resulting solid residue was triturated with water and filtered to afford the product as a brown crystalline solid (36 mg, 50 % yield). Mp = 235-240°C. MS ( $M + 1$ ) = 397 m/z.

**Example 21**

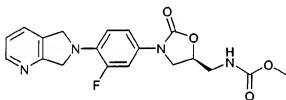
25



Compound 16

To the amide (prepared in Example 20) (36 mg, 0.09 mmol) suspended in  $\text{CH}_2\text{Cl}_2$  (1.0 mL), was added  $\text{MnO}_2$  (three portions of 100 mg over three days) at rt. The reaction mixture was filtered through a plug of Celite, washed with  $\text{CH}_2\text{Cl}_2$  (10 mL), and concentrated under reduced pressure to afford the product as an off-white crystalline solid (3 mg, 8 % yield). MS ( $M + 1$ ) = 395 m/z.

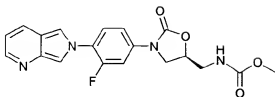
#### 10 Example 22



Compound 17

To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added dropwise methyl chloroformate (120 mg, 1.27 mmols). After stirring for four hours at rt, the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over  $\text{MgSO}_4$ , filtered, and concentrated to provide an oil which was triturated with ether to afford a brown crystalline solid (35 mg, 50% yield). MS ( $M + 1$ ) = 387 m/z.

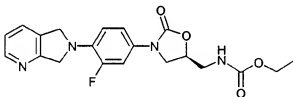
#### Example 23



Compound 18

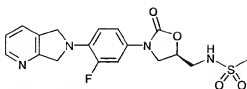
- To the carbamate (prepared in Example 22) (33 mg, 0.08 mmol) suspended in  $\text{CH}_2\text{Cl}_2$  (1.0 mL), was added  $\text{MnO}_2$  (150 mg). After stirring overnight at rt the reaction mixture was filtered through a plug of Celite, washed with  $\text{CH}_2\text{Cl}_2$  (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (6.0 mg, 18% yield). MS ( $M + 1$ ) = 385 m/z.

**Example 24**



Compound 19

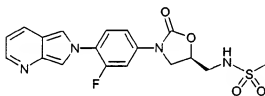
- To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL) was added dropwise ethyl chloroformate (0.1 mL, 1.04 mmols). After stirring overnight at rt the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over  $\text{MgSO}_4$ , filtered, and concentrated. The resulting semi-solid was treated with water, filtered and air-dried to afford a brown crystalline solid (18 mg, 30% yield). MS ( $M + 1$ ) = 401 m/z.

**Example 25**

Compound 20

- 5 To the amine (prepared in Example 8) (95 mg, 0.29 mmol) suspended in pyridine (0.5 mL) was added methane sulfonylchloride (0.08 mL, 1.0 mmol). After stirring overnight at rt the pyridine was removed under a stream of nitrogen. The residue was treated with water, filtered and air-dried to afford a brown solid (45 mg, 38% yield). Mp = 172-176 °C. MS (M + 1) = 407 m/z.

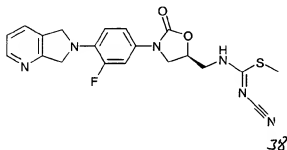
10

**Example 26**

Compound 21

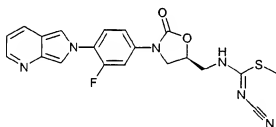
- 15 To the sulfonamide (prepared in Example 25) (10 mg, 0.02 mmol) suspended in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL), was added MnO<sub>2</sub> (100 mg, 10 mmols). After stirring overnight the reaction mixture was filtered through a plug of Celite, washed with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and concentrated under reduced pressure to afford the product as a brown crystalline solid (0.5 mg, 5% yield). MS (M + 1) = 405 m/z.

20

**Example 27**

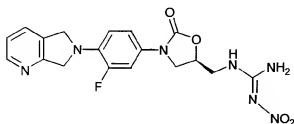
## Compound 22

To the amine (prepared in Example 8) (200 mg, 0.61 mmol) suspended in toluene (8 mL), was added dimethyl-N-cyanodithioiminocarbonate (89 mg, 0.61 mmol). After stirring overnight at reflux the toluene was decanted and the oily residue treated with methanol, filtered, and air-dried to afford a brown crystalline solid (62 mg, 20% yield). Mp = 204-207°C. MS (M + 1) = 427 m/z.

**Example 28**

## Compound 23

A suspension of the thioimide (from Example 27) (45 mg, 0.10 mmol) and MnO<sub>2</sub> (200 mg, 2.0 mmols) in CH<sub>2</sub>Cl<sub>2</sub> were stirred at rt for one day whereupon a second addition of MnO<sub>2</sub> (150 mg, 1.5 mmols) was added. After an additional day of stirring the mixture was filtered through Celite, washed with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), concentrated to afford a yellow crystalline solid (20 mg, 45% yield). MS (M + 1) = 426 m/z.

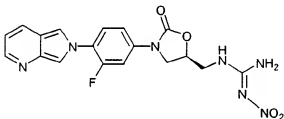
**Example 29**

## Compound 24



A suspension of the amine (prepared in Example 8) (165 mg, 0.5 mmol) and 2-methyl-1-nitro-2-thiopseudourea (94 mg, 0.70 mmol) (as prepared as in EP 0539204/ 1993) in methanol (2 mL) was refluxed for four hours. After cooling to rt the reaction mixture was filtered and air dried to afford a yellow crystalline solid (50 mg, 24% yield). Mp = 202-206 °C. MS (M + 1) = 416 m/z.

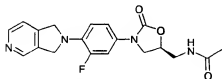
### Example 30



Compound 25

To the nitroguanidine (prepared in Example 29) (35 mg, 0.08 mmol) suspended in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) was added  $\text{MnO}_2$  (three additions of 100 mg over three days). The reaction mixture was filtered through a plug of Celite, washed with  $\text{CH}_2\text{Cl}_2$  (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (1.6 mg, 4% yield). MS (M + 1) = 414 m/z.

### Example 31

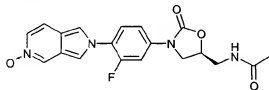


Compound 26

The starting material 6,7-dihydro-5H-pyrrolo[3,4-c]pyridine was prepared as in US Pat. No. 5,371,090 to Petersen et al. Compound 26 was then prepared as

in Example 8 except the acetamide was recrystallized from acetonitrile to give a light tan solid.  $M_p = 182-190^{\circ}\text{C}$  decomposition.  $MS (M + 1) = 371\text{ m/z}$ .

### Example 32



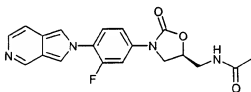
5

Compound 27

Compound 27 was isolated from the final step of Example 31 via chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent) of the mother liquors collected from recrystallization. Light yellow solid,  $M_p = 219-225^{\circ}\text{C}$  decomp.  $MS (M + 1) = 385\text{ m/z}$ .

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### Example 33



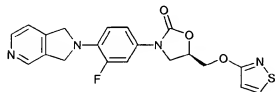
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Compound 28

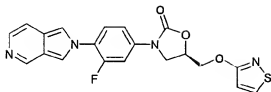
Compound 28 was prepared as in Example 9 except with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent. Light yellow solid,  $M_p = 219-225^{\circ}\text{C}$  decomposition.  $MS (M + 1) = 369\text{ m/z}$ .

20

### Example 34



Compound 29



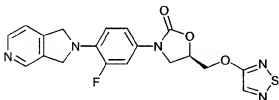
Compound 30

- 5 Isothiazole (0.088 g, 0.87mmol)(prepared as in *J Heterocyclic Chem* **1971**, 8, 591) was added portionwise at rt to a suspension of sodium hydride (0.036 g, 0.91 mmol, 60% in oil) in DMF (4 mL) under nitrogen. The mixture was stirred for 30 minutes whereupon the mesylate from Example 31 (0.31 g, 0.76 mmol), in DMF (10 mL), was added all at once. After stirring for 6 hours at 60 °C the
- 10 reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 5% MeOH/EtOAc as eluent. Two products were isolated from the chromatography: 0.050g of
- 15 Compound 29; and 0.022 g of Compound 30. Overall yield, 30%.

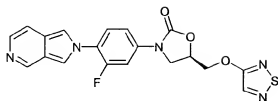
Compound 29 MS (M+1) = 413.0

Compound 30 MS (M+1) = 411.1

## 20 Example 35



Compound 31



Compound 32

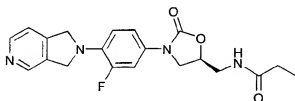
5

To a suspension of sodium hydride (0.036 g, 0.91mmol, 60% in oil) in DMF (4 mL) at rt under nitrogen was added portion wise 4-hydroxy-1, 2, 5-thiadiazole (0.088 g, 0.87 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]). After stirring for 30 min the mesylate from Example 31 (0.310 g, 0.76 mmol), in  
10 DMF (10 mL), was added all at once. After stirring for 6 hours at 60 °C the reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 2% MeOH/EtOAc as  
15 eluent. Two products were isolated from the chromatography: 0.035 g of Compound 31; and 0.0093 g of Compound 32. Overall yield, 14%.

Compound 31 MS (M+1) = 414.0

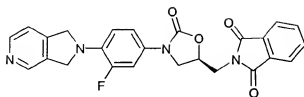
Compound 32 MS (M+1) = 412.1

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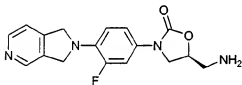
**Example 36**

Compound 33

## Step 1:



- To the mesylate from Example 31 (2.45 g, 6.01 mmol) dissolved in degassed DMF (100 mL) under nitrogen was added potassium phthalimide (2.23 g, 12.0 mmols). After heating at 65 °C for 3 hours the reaction mixture was cooled, poured into water (300 mL), and extracted with methylene chloride (3x200 mL). The combined organics were washed with water (3x150 mL) dried over sodium sulfate, concentrated to a tan solid. This solid was washed with water and dried in a high vacuum oven at 50 °C to afford 2.20 g (80%) of the oxazolidinone phthalimide. MS= 459.1 (M+1)



## Step 2:

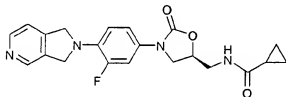
- To the above phthalimide (0.97 g, 2.1 mmols) in degassed methanol (30 mL) under nitrogen was added hydrazine monohydrate (0.2 mL, 4.3 mmols) dropwise. After refluxing for 12 hours the reaction mixture was cooled to rt, and concentrated, suspended in  $\text{CH}_2\text{Cl}_2$  and filtered. The crude oxazolidinone amine was concentrated and used without further purification.

## Step 3:

## Compound 33,

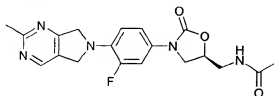
To the crude amine (0.14 g, 0.44 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added pyridine (0.14 mL, 1.8 mmols) followed by propionyl chloride (0.76 mL, 0.88 mmol).

- After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using neat EtOAc as eluent to afford the propionyl amide as a gold oil (0.020 g, 12% yield). MS= 385.2 (M+1)

**Example 37**

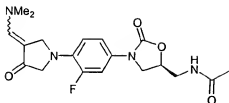
10 Compound 34

- To the crude amine (as prepared in Example 36) (0.144 g, 0.437 mmol) in methylene chloride (5 mL) was added pyridine (0.14 mL, 1.7 mmols), followed by cyclopropane carbonyl chloride (0.08 mL, 0.88 mmol). After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using a gradient elution of 1% to 5% to 10% MeOH/ EtOAc. The desired product eluted with 5% MeOH/ EtOAc and was concentration to afford the product as a white powder (0.012 g, 7% yield). MS= 397.2 (M+1)

25 **Example 38**

Compound 35

Step 1:



5

To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.150 g, 0.447 mmols) was added methoxy-bis(dimethylamino)methane (1 mL). After heating at 50 °C for 15 min the reaction mixture was concentrated to provide the crude  $\beta$ -ketoenamine which was used without further purification.

10

Step 2;

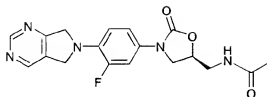
Compound 35

To ethanolic NaOEt (made from 0.027 g Na in 3 mL EtOH) was added acetamidine hydrochloride (0.113 g, 1.19 mmols) and the above  $\beta$ -ketoenamine oxazolidinone acetamide. After refluxing for 3 hrs the reaction mixture was cooled to rt, concentrated, taken up in chloroform, and washed with water (3x8 mL). After drying over sodium sulfate the crude product was concentrated, dissolved in 5% MeOH/ EtOAc, and filtered to afford the product as an off-white solid (0.052 g, 45% yield). Mp = 234 °C, decomp. MS = 385.9 (M+1)

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25

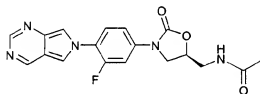
Example 39



Compound 36

To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.099 g, 0.29 mmol) was added methoxy-bis(dimethylamino)methane (1.0 mL). After heating at 50 °C for 2 hrs the reaction mixture was concentrated to provide the crude  $\beta$ -ketoenamine. To this mixture was added benzene (5 mL), DMF (1 mL) and formamidinium acetate (0.55 g, 5.3 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a white powder (0.037 g, 34% yield). Mp = 230-232 °C. MS (M + 1) = 372 m/z.

15

**Example 40**

Compound 37

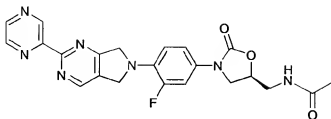
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The above acetamide from Example 39 (0.020 mg, 0.054 mmol) was taken up in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and MnO<sub>2</sub> added (0.10 g, 0.98 mmol). After stirring overnight at rt the reaction mixture was filtered through Celite and concentrated to afford the product as a light yellow solid (0.016 g, 80% yield). Mp = 164-166 °C. MS (M + 1) = 370 m/z.

25

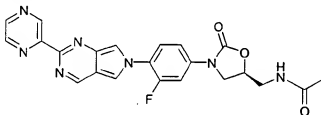
**Example 41**



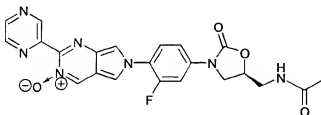


Compound 38

- 5 To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and pyrazine-2-carboxamidine hydrochloride (0.62 g, 3.9 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a light yellow solid (0.0026 g, 2% yield). Mp = 212-214 °C. MS (M + 1) = 450 m/z.

**Example 42**

15 Compound 39



Compound 40

- 20 The above acetamide from Example 39 (0.040 g, 0.088 mmols) was taken up in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and MnO<sub>2</sub> (0.36 g, 3.5 mmols) added in three portions over three days. After stirring for three days the reaction mixture was filtered through Celite, concentrated and chromatography on silica with 7%

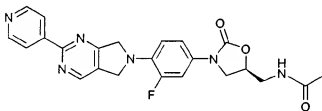
MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent. Two products were isolated from the chromatography: 0.001 g of Compound 39 as a light yellow solid (4% yield); and 0.002 g of Compound 40 as a yellow solid (4% yield).

5 Compound 39: MS (M + 1) = 448 m/z.

Compound 40: MS (M + 1) = 464 m/z.

### Example 43

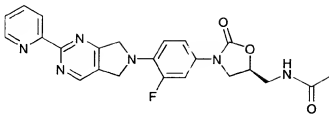
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Compound 41

15 To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 4-amidinopyridine hydrochloride (0.81 g, 5.2 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>  
20 as eluent to afford the product as a light yellow solid (0.072 g, 55% yield). Mp = 245-250 °C, decomp. MS (M + 1) = 449 m/z.

### 25 Example 44

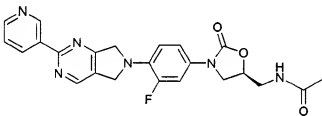


#### Compound 42

- 5 To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 2-aminopyridine hydrochloride (0.61 g, 3.9 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a yellow powder (0.054 g, 40% yield). Mp = 216-220 °C. MS (M + 1) = 449 m/z.
- 10

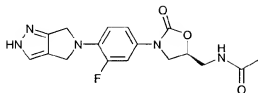
#### Example 45

15



#### Compound 43

- To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and 3-aminopyridine hydrochloride (0.49 g, 3.1 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a light purple, crystalline solid (0.044 g, 33% yield). Mp = 265-270 °C, decomp. MS (M + 1) = 449 m/z.
- 20
- 25

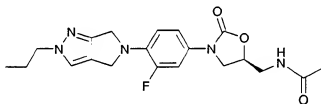
**Example 46**

5

**Compound 44**

To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and hydrazine hydrochloride (0.22 g, 3.2 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as off-white powder (0.022 g, 21% yield). Mp = 244-247 °C, decomp. MS (M + 1) = 360 m/z.

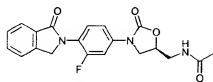
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**Example 47****Compound 45**

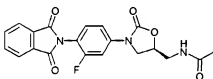
20

To the  $\beta$ -ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and n-propylhydrazine oxalate (0.87 g, 5.3 mmols). After heating overnight at 95 °C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50 °C), and chromatographed on silica with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the product as a light yellow solid (0.081 g, 55% yield). Mp = 204-208 °C. MS (M + 1) = 402 m/z.

25

**Example 48****Compound 46**

The starting material aniline (N-[[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide) was prepared as in World Patent WO 96/23788. To phthalic dicarboxaldehyde (0.0522 g, 0.378 mmol) in acetonitrile (1 mL) was added glacial acetic acid (0.05 mL, 0.87 mmol) and then the above aniline (0.0955 g, 0.357 mmol) in acetonitrile (5 mL) dropwise. After 4 hrs water (10 mL) was added and a precipitate was collected on a filter and washed with water and ether to provide Compound 46 as a light green solid (0.0655g, 48%). Mp = 211-214 °C. MS (M + 1) = 384 m/z.

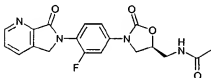
**Example 49****Compound 47**

To starting material aniline (N-[[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide)(0.095 g, 0.36 mmol)(as prepared in World Patent WO 96/23788) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added triethylamine (0.15 mL, 1.1 mmols) and phthaloyl dichloride (0.056 mL, 0.39 mmol). After stirring overnight a solid was collected on a filter, washed with water (10 mL) and

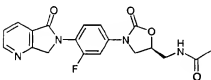
dried in vacuum oven (50 °C) to afford the product as a off-white solid (0.060, 42%). Mp = 240-242 °C. MS (M + 1) = 398 m/z.

### Example 50

5



### Compound 48



10 Compound 49

To starting material aniline (N-[[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide](0.20 g, 0.75 mmol)(as prepared in World Patent WO 96/23788) in acetonitrile (5 mL) was added 2,3-pyridine 15 dicarboxaldehyde (0.10 g, 6.6 mmols) and glacial acetic acid (0.050 mL, 0.87 mmol). After stirring for 5hrs the reaction mixture was concentrated and chromatographed on silica with 2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford the two products: 0.035 g of Compound 52 (12%) as a yellow solid; and 0.011 g of Compound 53 (4%) as a yellow solid.

20

Compound 48: Mp = 230-232°C. MS (M + 1) = 385 m/z.

Compound 49: Mp = 207-209°C. MS (M + 1) = 385 m/z.

25

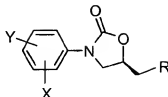
The invention has been described in detail with particular reference to the above embodiments thereof. The above embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent, to those skilled in the art, other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. It will be understood that variations and modifications can be effected within the spirit and scope of the invention; therefore, the instant invention should be limited only by the appended claims.

10

CLAIMS

We claim:

1. A compound of Formula I



Formula I

wherein:

R is selected from the group consisting of OH, O-Aryl, O-Heteroaryl, N<sub>3</sub>, OR', OSO<sub>2</sub>R'', -NR'''R''', or



wherein:

- (i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;
- (ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and
- (iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by cyano or alkoxy carbonyl having up to 4 carbon atoms, -CO<sub>2</sub>-R<sub>1</sub>, -CO-R<sub>1</sub>, -CO-SR<sub>1</sub>, -CS-R<sub>1</sub>, P(O)(OR<sub>2</sub>)(OR<sub>3</sub>), and -SO<sub>2</sub>-R<sub>4</sub>, in which

R<sub>1</sub> is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl or acyl having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon



atoms, said alkyl optionally substituted by straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen atoms, and -NR<sub>5</sub> R<sub>6</sub> in which R<sub>5</sub> and R<sub>6</sub> are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;

R<sub>2</sub> and R<sub>3</sub> are identical or different and are selected from hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms; and

R<sub>4</sub> is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

R<sub>4a</sub> is CN, COR<sub>4c</sub>, COOR<sub>4c</sub>, CONHR<sub>4c</sub>, CO-NR<sub>4c</sub> R<sub>4d</sub>, SO<sub>2</sub>R<sub>4c</sub>, SO<sub>2</sub>NHR<sub>4c</sub>, SO<sub>2</sub>-NR<sub>4c</sub> R<sub>4d</sub>, or NO<sub>2</sub>;

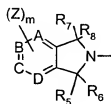
R<sub>4b</sub> is H, alkyl, OR<sub>4c</sub>, SR<sub>4c</sub>, amino, NHR<sub>4c</sub>, NR<sub>4c</sub>, R<sub>4d</sub>, (C1-C8), alkylaryl or mono-, di-, tri-, and per-halo(C1-C8) alkyl;

R<sub>4c</sub> and R<sub>4d</sub> are independently selected from H, alkyl, aryl, or in the case of any NR<sub>4c</sub>R<sub>4d</sub> group R<sub>4c</sub> and R<sub>4d</sub> taken together with the nitrogen atom to which they are attached form an unsubstituted or substituted pyrrolidiny, piperidiny or morpholiny group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub> alkoxy, thio-C<sub>1-8</sub>-alkyl, C<sub>1-8</sub> alkyl-amino, di(C<sub>1-8</sub>-alkyl)-amino, formyl, carboxy, alkoxy carbonyl, C<sub>1-8</sub> alkyl-CO-O-, C<sub>1-8</sub> alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, C<sub>3-6</sub> cycloalkyl, C<sub>1-8</sub> alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, C<sub>1-8</sub> alkoxy and C<sub>1-8</sub> acyloxy; and

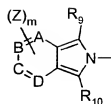
Y is a radical of Formulae II or III:

5



10

Formula II



Formula III

wherein

15  $R_5$ ,  $R_6$ ,  $R_7$ , and  $R_8$  are each independently H, alkyl, CN, nitro,  $C_{1-8}$  alkyl, halo- $C_{1-8}$ -alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, or substituted-heteroaryl, or  $R_5$  and  $R_6$  and/or  $R_7$  and  $R_8$  together form an oxo group;

20  $R_9$ , and  $R_{10}$  are each independently H, halogen, alkyl, OH, CN, mercapto, nitro,  $C_{1-8}$  alkyl, halo- $C_{1-8}$ -alkyl,  $C_{1-8}$  alkoxy, thio- $C_{1-8}$ -alkyl, amino,  $C_{1-8}$ -alkyl-amino, di( $C_{1-8}$ -alkyl-)amino, formyl, carboxy, alkoxycarbonyl,  $C_{1-8}$ -alkyl-CO-O-,  $C_{1-8}$ -alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, alkoxy, heteroaryl, substituted-heteroaryl, or amine ;

25

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O,  
30 and N;

Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl where dialkylamino is selected from dimethylamine, diethylamine,

morpholinyl, thiomorpholinyl, pyrrolidinyl, or piperidinyl, or, alkoxy, or NHCO-(C<sub>1</sub>-C<sub>8</sub>-alkyl); and

m is 0 or 1,

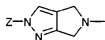
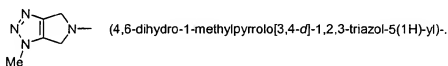
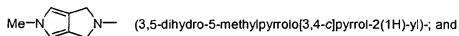
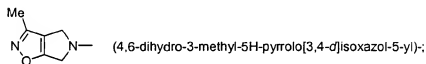
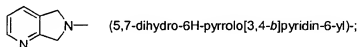
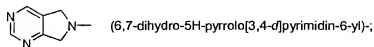
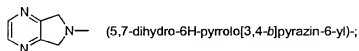
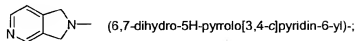
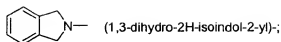
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and the pharmaceutically acceptable salts and esters thereof.

- 10 2. The compound of claim 1 wherein Y is selected from the group consisting of



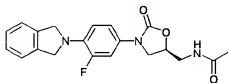
isindolone-;



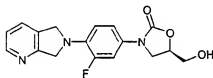
3. The compound of claim 1 wherein R is -NHCOCH<sub>3</sub> or is selected from the group consisting of



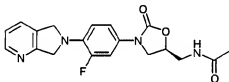
4. A compound of Claim 1 having the formula:



5. A compound of Claim 1 having the formula:

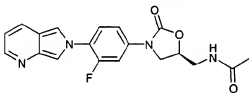


6. A compound of Claim 1 having the formula:



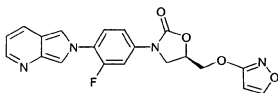
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7. A compound of Claim 1 having the formula:

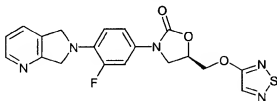


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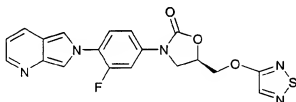
8. A compound of Claim 1 having the formula:



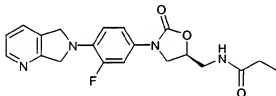
9. A compound of Claim 1 having the formula:



5 10. A compound of Claim 1 having the formula:

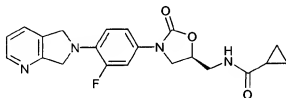


11. A compound of Claim 1 having the formula:



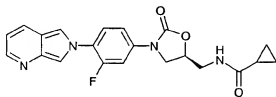
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12. A compound of Claim 1 having the formula:



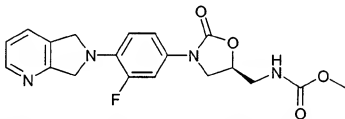
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- 5 13. A compound of Claim 1 having the formula:

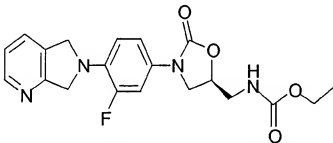


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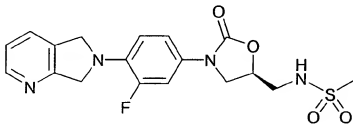
14. A compound of Claim 1 having the formula:



15. A compound of Claim 1 having the formula:

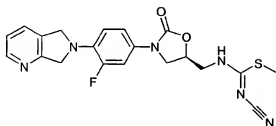


16. A compound of Claim 1 having the formula:



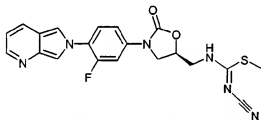


- 5 17. A compound of Claim 1 having the formula:

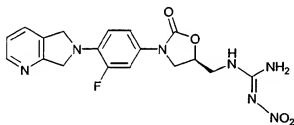


18. A compound of Claim 1 having the formula:

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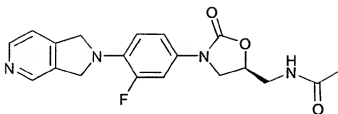


19. A compound of Claim 1 having the formula:

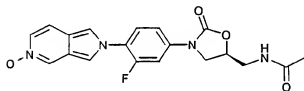


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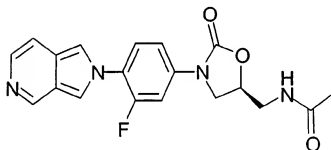
20. A compound of Claim 1 having the formula:



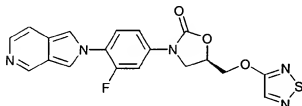
21. A compound of Claim 1 having the formula:



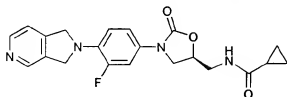
22. A compound of Claim 1 having the formula:



23. A compound of Claim 1 having the formula:

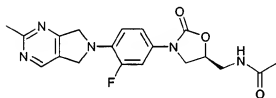


24. A compound of Claim 1 having the formula:

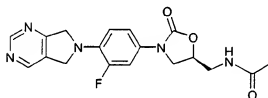


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10 25. A compound of Claim 1 having the formula:

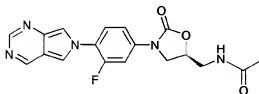


26. A compound of Claim 1 having the formula:



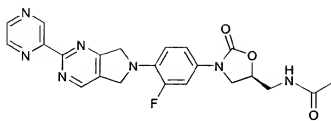
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27. A compound of Claim 1 having the formula:

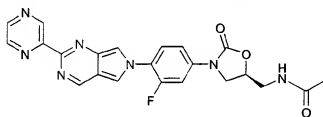


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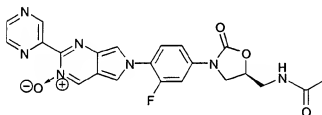
28. A compound of Claim 1 having the formula:



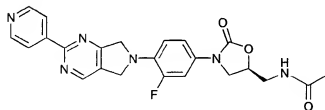
- 5 29. A compound of Claim 1 having the formula:



- 10 30. A compound of Claim 1 having the formula:

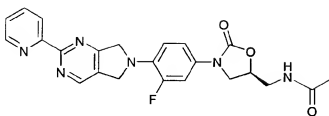


31. A compound of Claim 1 having the formula:

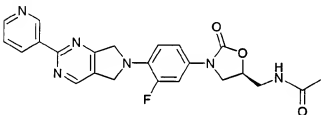


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32. A compound of Claim 1 having the formula:

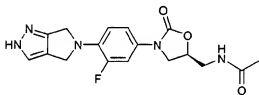


33. A compound of Claim 1 having the formula:



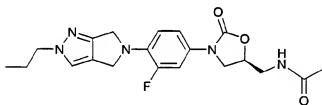
5

34. A compound of Claim 1 having the formula:



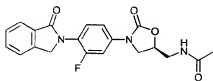
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35. A compound of Claim 1 having the formula:

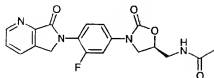


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36. A compound of Claim 1 having the formula:

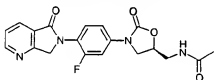


37. A compound of Claim 1 having the formula:



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38. A compound of Claim 1 having the formula:



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39. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

40. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound according to Claim 1.

41. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective dose of the pharmaceutical composition of a compound according to Claim 1.

42. The method of Claim 40 or 41 wherein said condition is selected from the group consisting of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections and hospital-acquired lung infections.

43. The method of Claim 40 or 41 wherein said bacterium is selected from the group consisting of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *S. pyogenes*, *Enterococcus spp.*, *Moraxella catarrhalis* and *H. influenzae*.

- 5 44. The method of Claim 40 or 41 wherein said bacterium is a Gram-positive coccus.

45. The method of Claim 44 wherein said Gram-positive coccus is drug-resistant.

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 00/21093

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/10 C07D471/04 C07D487/04 C07D498/04 A61K31/422  
A61K31/437 A61K31/4985 A61K31/519 A61K31/424 A61P31/04  
/(C07D471/04, 221:00, 209:00), (C07D487/04, 231:00, 209:00),

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	DATABASE WPI Section Ch. Week 200006 Derwent Publications Ltd., London, GB; Class B03, AN 2000-069004 XP002154332 - & JP 11 322729 A (HOKURIKU PHARM CO LTD), 24 November 1999 (1999-11-24) abstract; particularly page 43, no 130, page 51, no 170, page 60, no 212, page 75, no 278 and page 88, no 56 of the original document ---	1-45
Y	WO 96 23788 A (PHARMACIA + UPJOHN COMPANY) 8 August 1996 (1996-08-08) cited in the application the whole document --- -/--	1-45

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

1 December 2000

Date of mailing of the international search report

14/12/2000

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# INTERNATIONAL SEARCH REPORT

International Application No  
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## A. CLASSIFICATION OF SUBJECT MATTER

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(C07D487/04, 209:00, 209:00), (C07D487/04, 249:00, 209:00),  
(C07D487/04, 239:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 10342 A (ZENECA LIMITED) 4 March 1999 (1999-03-04) the whole document ----	1, 39-45
A	WO 96 35691 A (PHARMACIA & UPJOHN COMPANY) 14 November 1996 (1996-11-14) the whole document ----	1, 39-45
A	WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996 (1996-05-23) the whole document -----	1, 39-45

☐ Further documents are listed in the continuation of box C.

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- \*S\* document member of the same patent family

Date of the actual completion of the international search

1 December 2000

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/21093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11322729 A	24-11-1999	NONE	
WO 9623788 A	08-08-1996	AU 703465 B AU 4899896 A BR 9607017 A CA 2208603 A CN 1172484 A CZ 9702314 A EP 0807112 A FI 973217 A JP 10513446 T NO 973550 A NZ 302844 A PL 321663 A US 6124334 A US 5910504 A	25-03-1999 21-08-1996 28-10-1997 08-08-1996 04-02-1998 12-08-1998 19-11-1997 04-08-1997 22-12-1998 03-10-1997 29-06-1999 22-12-1997 26-09-2000 08-06-1999
WO 9910342 A	04-03-1999	EP 1005468 A	07-06-2000
WO 9635691 A	14-11-1996	AU 702752 B AU 5484996 A CA 2218088 A CN 1184481 A EP 0828741 A FI 974180 A JP 11506430 T NO 975158 A US 6090820 A	04-03-1999 29-11-1996 14-11-1996 10-06-1998 18-03-1998 10-11-1997 08-06-1999 09-01-1998 18-07-2000
WO 9615130 A	23-05-1996	AU 702733 B AU 3889095 A BR 9509673 A CN 1163615 A, B EP 0792273 A JP 10508844 T NO 972222 A NZ 295528 A RU 2128660 C US 5952324 A	04-03-1999 06-06-1996 30-09-1997 29-10-1997 03-09-1997 02-09-1998 14-05-1997 29-03-1999 10-04-1999 14-09-1999